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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/340,595	06/28/1999	OSVALDO LUIS PODHAJCER	1581.0300002	4148

7590 03/26/2003

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EXAMINER
SCHMIDT, MARY M

ART UNIT	PAPER NUMBER
1635	74

DATE MAILED: 03/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Application No.	Applicant(s)
09/340,595	PODHAJCER ET AL.
Examiner	**Art Unit**
Mary M. Schmidt	1635

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-8,15-17,37 and 39-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-8,15-17,37 and 39-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 June 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *23*.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 15-17, 39-42 and 44-54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treatment of human melanoma tumors subcutaneously in humans and mice via administration o the SPARC antisense shown in the specification as filed, and methods if inhibiting SEQ ID NO:1, human SPARC, via adminstration of said antisense in cells in cell culture (*in vitro*), does not reasonably provide enablement for methods of administration of any SPARC inhibitor for any treatment as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

New claims 39-42 are drawn to methods of treatment of a tumor in a human comprising administering to cells of the tumor a nucleic acid molecule comprising a sequence that binds a polynucleotide comprising SEQ ID NO:1 where in the nucleic acid molecule has the function of preventing or decreasing expression of human osteonectin.

New claims 44-49 are drawn to methods of treating a tumor that overexpresses osteonectin, comprising transfecting one or more cells of said tumor with a nucleic acid molecule comprising a sequence that binds to a polynucleotide comprising SEQ ID NO:1, wherein said nucleic acid molecule has the function of preventing or decreasing expression of osteonectin in said tumor cell.

New claims 50-54 are drawn to methods of killing tumor cells in an animal or human via administering a sequence which binds SEQ IDNO:1 and has the function of preventing or decreasing expression of osteonectin in the tumor cell.

The specification as filed teaches on page 1, last paragraph, that "The literature of oncology includes numerous mentions of osteonectin and its symptoms. In particular, reports form different laboratories indicate that osteonectin over-expression was associated with neoplastic progression of different malignant tumors..., including human melanoma. Porter et al.... previously reported increased SPARC expression in ovary cancer cells, but on the other hand Mock et al. have reported that SPARC expression is down-regulated in ovary cancer cells compared to normal cells...." On page 2, the specification states other reported effects of osteonectin such as having effects on tumor cell adhesion and invasion, and a correlation to lung colonization by tumors.

The specification describes on page 12 that "SPARC (osteonectin) antisense expression is conveniently obtained from a 1.6kb cDNA for SPARC extending for example from nucleotide 15 to nucleotide 1689 of the sequence given by Swaroop et al." The specification states on page 15

that other antisense, at least about 12 nucleotides complementary in sequence to the sequence of the chosen osteonectin target may be used.

The specification teaches administration *ex vivo* of human HB-MEL- melanoma cells having the antisense to SPARC inside (expressed from a CMV promoter) and showing reduced SPARC expression levels as taught on page 17 of the specification, to mice. Page 22 of the specification as filed teaches in Table X the results of the mice that were injected with the cells in the left flank subcutaneously. As stated on page 24, these experiments showed the ability to prevent tumor formation in mice having the SPARC antisense melanoma cells. A bystander effect was also noticed: "This effect was accompanied by a localized and massive recruitment of PMNLs which were probably responsible for tumor cell rejection. In the work described below we use coinoculation of these genetically modified cells with parental cells to induce an *in vivo* dominant bystander effect leading to the elimination of parental cells." (Example 2) On page 28, the results of this experiment showed that a 1:1 mixture of tagged-parental cells (expressing beta-gal, but no SPARC antisense) and the SPARC antisense cells showed no tumor growth compared to the tagged-parental cells and non-modified cells alone. See Table 3, page 32. In conclusion, the specification teaches on page 32 that "[d]ownregulation of SPARC completely prevented tumor formation in nude mice and induced a dominant "bystander" effect leading to the elimination of parental cells expressing SPARC. Since no direct effect of SPARC antisense transfected cells on parental cells was observed, the evidence indicate that in the recited

embodiments of the invention PMNLs recruitment and activation was responsible for the bystander killing of parental human melanoma cells."

While the specification as filed is considered enabling for treatment of human melanoma tumors subcutaneously in humans and mice via administration of the SPARC antisense shown in the specification as filed, such results are not considered predictive nor enabling for treatment of other tumors, nor use of other inhibitors of SPARC (SEQ ID NO:1). As admitted by the specification and reiterated above, the role of SPARC osteonectin is different in different cell types and opposing results are found in the literature for the expected result of use of antisense versus sense expression in ovary cancer cells. Since there is no nexus taught in either the specification as filed or the prior art for how to administer SPARC antisense or other inhibitors to treat other types of tumors, one of skill in the art would necessarily practice *de novo* "trial and error" experimentation to discern the treatment potentials of other types of cancers.

Furthermore, the nearly full-length SPARC antisense taught in the specification as filed is not considered representative of design and use of any other SPARC antisense to SEQ ID NO:1 for the claimed treatment effects since each antisense must be evaluated on an antisense-by-antisense basis for uses in vivo due to the high level of unpredictability in the art shown below. The use of the antisense to SPARC is not considered enabling for design of a ribozyme or other type of inhibitor to SEQ ID NO:1 since they would also have individual design criteria not addressed by the instant specification as filed as having a specific nexus to an expectation of success *in vivo*.

When designing an antisense oligonucleotide for administration to a whole organism such as the instantly claimed antisense to human SPARC osteonectin receptor, the following general factors must be considered: (1) specificity to the target molecule, (2) effective concentration without toxicity, (3) stability of the drug agent in the whole organism. The specification does not provide any specific guidance to the skilled artisan as to how to design antisense that are specific to SPARC osteonectin and stable in a whole organism context for the claimed functions.

The factors considered barriers to successful delivery of antisense oligonucleotide delivery in the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Note also Ma et al. who teach (on page 167) that "to gain therapeutic advantage using antisense-based technology, ODNs must have certain characteristics. They must be resistant to degradation, internalize efficiently, hybridize in a sequence specific manner with the target nucleic acid, display adequate bioavailability with a favorable pharmacokinetics profile and be nontoxic." Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained. Flanagan teaches, "oligonucleotides (*in vivo*) are not distributed and internalized equally among organs and tissues.... Unfortunantly, therapeutically important sites such as solid tumors contain very little

oligonucleotide following intravenous injections in animals (page 51, column 2)." Ma et al. supports the difficulties of *in vivo* use of ODNs on pages 160-172. Jen et al. further taught that "given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive. While a number of phase I II trials employing ONs have been reported..., virtually all have been characterized by a lack of toxicity but only modest clinical effects." (Page 315, col. 2) Green et al. summarizes that "the future of nucleic acid therapeutics using antisense ODNs ultimately depends on overcoming the problems of potency, stability, and toxicity; the complexity of these tasks should now be apparent. Improvements in delivery systems and chemical modifications may lead to safer and more efficacious antisense compounds with improved pharmacokinetics and reduced toxicities." (P. 103, col. B) Note also some of the major outstanding questions that remain in the art taught by Agrawal et al. on page 79, col. 2.

In vitro, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Note also Ma et al. who teach that "*in vitro* subcellular distribution is dependent on the type of ODN modification, cellular system and experimental conditions. ODNs, once internalized, are distributed to a variety of subcellular compartments." (Page 168) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which

inhibits a target *in vivo*: it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." Note Jen et al. who teach that "although mRNA targeting is impeccable in theory, many additional considerations must be taken into account in applying these strategies in living cells including mRNA site selection, drug delivery and intracellular localization of the antisense agent." (Abstract) Bennett et al. further taught that "although the antisense paradigm holds great promise, the field is still in its early stages, and there are a number of key questions that need to be answered and technical hurdles that must be overcome....The key issues concerning this class of chemicals center on whether these compounds have acceptable properties as drugs. These include pharmacokinetics, pharmacological and toxicological properties." (Page 13) As argued above, these issues remain unpredictable in the art for antisense oligonucleotide administration *in vivo*.

One of skill in the art would not accept on its face the successful use of the breadth of claimed SPARC/osteonectin antisense molecules *in vivo* and further, treatment effects, in view of the lack of guidance in the specification and the unpredictability in the art. Neither the specification nor technology today teach general guidelines for successful delivery or treatment effects of antisense molecules such as those claimed in whole organisms. Specifically the specification does not teach (1) stability of the antisense molecule *in vivo*, (2)effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment

effects. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by the specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed.

Response to Arguments

3. Applicant's arguments filed 1/3/03 have been fully considered but they are not persuasive.

. Applicant rebuts the previous rejection which was a full-lack of enablement rejection and not the modified scope of enablement rejection found above. Applicant states on page 12 of the response that "[t]he references referred to by the Examiner provide ample evidence that successful antisense therapies were in existence at the time of the priority date. One skilled in the art, given the identification of osteonectin as a suitable target and armed with the knowledge of sucessful antisense therapies as shown in the cited references, would have had no difficulty in practicing the presently claimed invention."

In response, new references have been cited teaching the unpredictability in the field of antisense therapeutics. The argument has been reevaluated based on these references that antisense effects in therapy must be ascertained in a case by case scenario, and there are no general rules or guidance to follow in the art for making any antisense successful in vivo for therapy uses. Applicants state on page 13 that "the specification provides ample direction as to how to determine whether a nucleic acid molecule decreases or prevents osteonectin expression,

for example, by Western blot using anti-SPARC antibodies. See Example 1 and Figure 1. The Examiner mis-characterizes this determination as "trial and error" experimentation. In fact, it is not undue experimentation at all. It is the kind of screening that is routinely practiced in the pharmaceutical industry. Given the teachings of the present specification, it would be entirely routine for one skilled in the art to construct nucleic acid molecules that bind to SEQ ID NO:1 and to determine which of them has the ability to decrease or prevent osteonectin expression and use them to treat a tumor. While many nucleic acid molecules may be tested, such testing is routinely performed in the pharmaceutical industry."

In response, the "routine screening" that applicant is referring to is testing many different potential antisense candidates for their ability to function *in vivo*. The claims are not drawn to methods of screening antisense, but rather are instead drawn to methods of treatment of tumors with antisense. As shown in the newly cited references above, success of an antisense in cells in cell culture, the most common screening technique, does not correlate to an expectation of success in use of the antisense in cells in vivo for therapeutic purposes. The ability to detect a protein via Western blot with an antibody as alluded to by applicant above does not further provide guidance for design of specific nucleic acid antisense sequences. Instead, it is simply a tool for determining protein concentration after the protein has been collected somehow. The examples in the specification as filed do not further provide guidance for making and using antisense other than the SPARC osteonectin antisense taught therein having the claimed functions.

Applicant further states that "the Examiner has failed to consider the impact of the "bystander effect" demonstrated in the present specification." The newly reformed scope of enablement rejection gives weight to this finding since methods of treatment of melanoma tumors with the SPARC antisense are now considered enabled.

4. Claims 15-17, 39-42 and 44-54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

MPEP 2163 teaches the following conditions for the analysis of the claimed invention at the time the invention was made in view of the teachings of the specification and level of skill in the art at the time the invention was made:

> The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence....A lack of written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process....Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement....The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by

functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

See the brief description of the claims and the teachings of the specification as filed stated above. Based on these teachings, one of skill in the art would not have been able to readily envisage a representative number of inhibitors (antisense, ribozyme or other types of inhibitors of the target gene SEQ ID NO:1) having the claimed treatment functions in the claimed methods, other than the SPARC osteonectin antisense inhibitor taught in the specification by way of example. The description of one antisense having a correlated treatment function to decrease melanoma cancer subcutaneously is not considered representative of a representative number of species of any SPARC inhibitor (antisense, ribozyme or other type) as broadly claimed having the breath of treatment effects in a whole organism upon administration. As reiterated above, "[a] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence...." Absent further specific nucleic acid sequence description that directly correlates to the claimed treatment effects, one of skill in the art would not readily envisage the nucleic acid sequence structure of any other SPARC nucleic acid inhibitor having the claimed treatment functions upon administration to a whole organism. As such, one of skill in the art would not have recognized that application was in possession of a

representative number of species of any SPARC osteonectin inhibitors at the time the invention was made.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 6-8, 37, 43 and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ledda et al. (*Medicina* Vol. 55:565-566, Abstract No. 267, Sociedad Argentina De Investigacion clinica, December 1995; IDS filed 2/3/03, reference AT/AR (English translation)) in view of GenEmbl database Accession No. J03040 (human SPARC/osteonectin mRNA, complete CDS., Jan. 1995), Baracchini et al. (U.S. Patent 5,801,154) and Ostrand-Rosenberg et al. (U.S. Patent 5,858,776).

New claim 43 is drawn to a composition comprising a nucleic acid molecule comprising a sequence that binds to a polynucleotide comprising SEQ ID NO:1 or a corresponding RNA sequence, wherein said nucleic acid has the function of preventing or decreasing expression in a cell of human osteonectin; and a pharmaceutically acceptable carrier. Claims 6-8 further specify

that the nucleic acid molecule is an antisense RNA molecule that binds to human osteonectin mRNA, the nucleic acid is conjugated to or administered in combination with a carrier molecule, the carrier molecule has a function selected from the group consisting of increasing the solubility of the nucleic acid molecule, increasing the uptake into a cell of the nucleic acid molecule, slowing the breakdown of the nucleic acid molecule, preventing the breakdown of the nucleic acid molecule, and facilitating the manufacture of the nucleic acid molecule. Claim 37 further states that the composition is a pharmaceutical composition. Claim 55 is drawn to a viral vector capable of transferring genetic material into a human cell, wherein said vector expresses a nucleic acid molecule comprising a sequence that binds to a polynucleotide comprising SEQ ID NO:1 or a corresponding RNA sequence, wherein said nucleic acid molecule has the function of preventing or decreasing expression of osteonectin in said tumor cell.

Ledda et al. is relied upon to teach design of antisense to SPARC expressed from a eukaryotic vector under the CMV promoter and transfected into human melanoma cells that are then *ex vivo* transfected into mice. 100% of the mice injected with the control cells developed a tumor, but none of the mice that were injected with cells expressing the SPARC antisense developed tumors. This reference does not further specify the size of the SPARC antisense (although it appears that it may have been a full-length antisense), nor expression from a viral vector. They further do not state that the antisense was delivered as a pharmaceutical composition with a carrier.

Baracchini et al. is relied upon to teach that it was well-known in the art at the time the invention was made to design antisense oligonucleotides to a desired target gene and to make pharmaceutical compositions of the antisense compounds including use of colloidal dispersion systems such as liposomes for delivery to cells (Baracchini et al. Col. 4, lines 23-64). They do not specifically teach use of a viral vector for expression of the antisense in cells.

Ostrand-Rosenberg et al. is relied upon to teach viral vectors that were known in the art as useful for administration to tumor cells, such as retroviral vectors, adenoviral vectors, adeno-associated viral vectors. They teach also that alternatively the naked nucleic acid may be directly injected to tumors of the melanoma using liposome carriers. See col. 7, lines 49-67.

It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to make antisense compositions to the human SPARC/osteonectin target gene of SEQ ID NO:1 since Ledda et al. provided motivation for design of antisense to the human SPARC/osteonectin gene, the target gene of SEQ ID NO:1 was known in the art (GenEmbl J03040), Baracchini et al. taught how to further design antisense to a known target gene, including use of pharmaceutically acceptable carriers complexed to the antisense. It would have been further *prima facie* obvious to substitute the vector taught by Ledda et al. for a viral vector since viral vectors were well-known in the art for administration to tumor cells as taught by Ostrand-Rosenberg et al.

One of ordinary skill in the art would have been motivated to design an antisense to human SPARC osteonectin gene of instant SEQ ID NO:1 since Ledda et al. taught motivation for design of antisense to SPARC osteonectin and the sequence of instant SEQ ID NO:1 was known in the art (GenEmbl J03040). One of ordinary skill in the art would have been motivated to design an antisense as taught by Barachinni et al. to a target gene by making antisense about 20-nucleic acids in length, having modifications for stability of the antisense in cells, and having a complex with a pharmaceutically acceptable carrier such as a liposome for improved delivery to the cell. One of ordinary skill in the art would have been further motivated to substitute the vector taught by Ledda et al. for a viral vector for delivery to tumor cells since such viral vectors were well-known in the art as taught by Ostrand-Rosenberg et al.

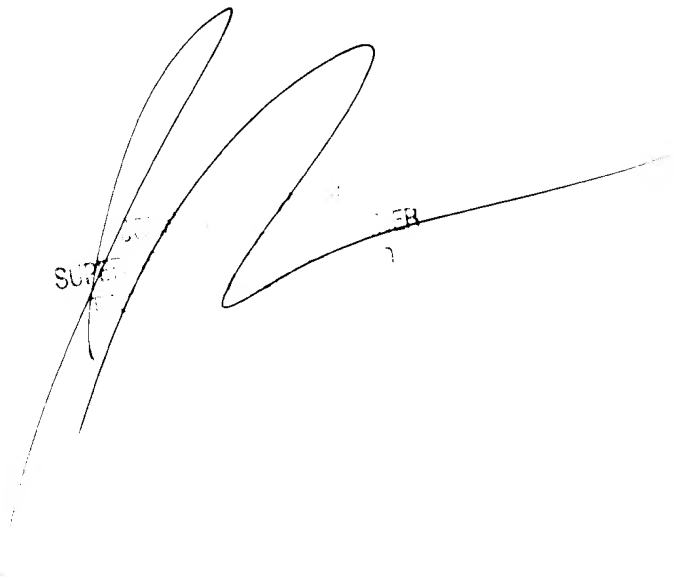
One of ordinary skill in the art would have had an expectation of success to make the instant compositions where the functions claimed, inhibition of human SPARC/osteonectin, are carried out in melanoma tumor cells in cell culture as taught by Ledda et al. for example.

7. Claims 15-17, 39-42 and 44-54 are considered free of the prior art since the claims are drawn to methods of treatment of tumors in a in a human *in vivo*, and the prior art did not teach nor fairly suggest methods of administration of SPARC osteonectin inhibitors for methods of treatment of tumors *in vivo* for the enabled scope of treatment of melanomas with the SPARC osteonectin antisense taught in the instant specification as filed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to Katrina Turner, whose telephone number is (703) 305-3413.



M. M. Schmidt
March 10, 2003